American Red Cross

National Headquarters

December 21, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Room 1-23
Rockville, MD 20852

RE: General Requirements for Blood, Blood Components, and Blood Derivatives; Notification of Deferred Donors; Proposed Rule. [64 Fed. Reg. 45355 (August 19, 1999) (Docket No. 98N-0607)]

Dear Docket Officer:

On behalf of the American Red Cross (ARC or Red Cross) I would like to thank you for the opportunity to comment on the Proposed Rule on Notification of Deferred Donors.

The proposal states:

> blood and plasma establishments would notify the donors that they have been deferred and the reason for the deferral; provide information concerning appropriate medical follow-up and counseling; describe the types of donations the donors should not make in the future; and discuss the possibility that the donor may be found suitable in the future, where appropriate.

The Red Cross, through its 37 Blood Services regions, supplies approximately 46% of the nation's blood component transfusion needs. Key to our efforts to maintain an adequate blood supply is a supportive and consistent relationship with those donors. Thus, the proposed regulation to establish and codify donor notification requirements is one which the Red Cross will seriously evaluate and, once final, insure full compliance.

Red Cross agrees with FDA that donors should be notified of their deferral status. Red Cross also believes that our current procedures for donor notification are consistent with the regulation's intent and we would like to describe our processes as they may help to refine the regulation's requirements. The attachment details ARC's recommendations

98N-0607

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about the additional requirements under consideration and asks for clarification of certain aspects of the proposal's intent including:

1. Responsibility of the Blood Establishment
2. Maximize flexibility
3. Notification of Donor Re-entry
4. Syphilis
5. Recommendations vs. Requirements
6. Evidence of Permanent Address
7. Permanent deferral due to donor suitability criteria
8. Donor Notification contact Requirements - Timing and methods
9. Notification for repeatedly Reactive (RR) on a single occasion for HTLV types I and/or II or for Anti-HBC
10. Deferral at Collection site
11. Cost Estimates

Again, Red Cross appreciates the opportunity to submit its views on the proposal. If there are any questions on this letter or the attachment, please contact Anita Ducca, Director, and Regulatory Relations, at 703-312-5601.

Sincerely,

Glenn M. Mattei, Esq.
Senior Director, Quality Assurance
and Regulatory Affairs
Biomedical Services
American Red Cross

Attachment

Comments by The American Red Cross on the FDA Proposed Regulation: General Requirements for Blood, Blood Components, and Blood Derivatives; Notification of Deferred Donors
[64 Fed. Reg. 45355 (Docket No. 98N-0607)]

1. Responsibility of the Blood Establishment

While well intended, the proposed regulation places an added responsibility on blood establishments that is inappropriate given our mission, our medical responsibilities and, indeed, our ethical responsibilities. It appears to press donor screening centers into serving as medical practice facilities, and places us in the position of performing public health services beyond current, reasonable expectations. For example, page 45359 describes donor counseling as follows:

> ...blood and plasma establishments would be required to provide information to deferred donors concerning appropriate medical follow-up and counseling. FDA currently recommends that this information include disease associations and possible modes of transmission as well as actions to be taken to minimize the risk of transmission. FDA believes that such information also would include referral to their own physician, or, where appropriate, the location of public health clinics as well as alternative testing and counseling centers.

In addition, proposed Section 630.6(b)(1) of the CFR states that the donor should be told "the reason for deferral".

Red Cross makes all attempts to provide as much information to the donor as is feasible given our knowledge of the screening questionnaire answers and the test results. Our assessment is limited to their suitability as a donor, and cannot be augmented by, for example, information that would be obtained through a medical exam or more sophisticated additional testing for diseases or symptoms related to the disease for which the donor tests positive. Thus, ARC requests that FDA indicate clearly that the counseling should only encompass what is known about the individual donor, either based solely on the screening questions or on test results, and that no further history, examination, or interpretation is anticipated.

We also request that FDA delete the discussion of providing a "referral to ... the location of public health clinics as well as alternative testing and counseling centers." Should such information be available to ARC, we would certainly share it with the donor, but only upon request and only if we believe our knowledge of such testing and centers is accurate. Our first recommendation will always be to urge donors to see their individual health care provider. Referral elsewhere may be perceived as a breach

of the patient/physician relationship. Referrals may also lead to other concerns such as the liability if, for example, a patient does not like the treatment they receive at a referred clinic or if the patient is not eligible for participation in the clinic for reasons that ARC could not be expected to know.

With regard to providing "the reason for their deferral including their screening test results of any approved supplemental... tests" (page 45358), Red Cross believes it is appropriate for a donor center to provide reasons for their deferral, but only on a limited basis. We believe this is intended to be an explanation limited to the test results and a possible interpretation of them. A blood establishment screens individuals for their suitability as blood donors. The questions and testing they perform are done solely for this purpose, not for diagnostic purposes. Thus, donor centers should not be expected to serve as a health care provider by including medical interpretations and/or specific diagnoses.

We also urge FDA to refrain from specifying additional forms of counseling that may be warranted. The setting and sensitivity of the notification should be factored into this recommendation. Specifically, some deferral notifications are made on site at the time of collection. Often, the counseling specified by FDA is either unwarranted or inappropriate at a collection site. For example, there may be cases where the donor reports lifestyle information that would preclude donation, and a donors' personal reactions to the deferral may make further counseling inadvisable. Indeed, the donor may find it presumptuous on the part of the collection center to "include ... actions to be taken to minimize the risk of transmission." (page 45359) We urge deletion of this statement from the final rule. At the collection site, ARC gives a deferred donor a letter with a general explanation of the reasons for deferral. We believe such a letter should be adequate to meet FDA's goals under this regulation.

Further, each individual donor may be a separate case requiring specific assessments before certain counseling should be provided, and it is inappropriate for the staff at the collection site to do so. Yet, the best assurance that the donor is informed of their donation status is to tell them at the time of donation so that there is no ambiguity about whether they received notification. In these cases, notification should be provided, but details on the reasons for deferral, and the need for further counseling should be made on a case by case basis, not mandated for all regardless of the circumstances.

2. Maximize flexibility

We also urge FDA to provide maximum flexibility in the mechanism for the actual notification. Section 630.6(b)(1) of the CFR states that the donor should be told "the reason for deferral". Although not specifically required, the proposal implies that the reasons should be specified in writing and in the first notification.

We believe, however, it is best to determine how much is provided in writing, and at what point in the notification process it is given, on a case by case basis. For some diseases, notification of positive test results could be of such concern to the donor, that we would not indicate details in writing. Rather, we prepare a general letter to the donor asking them to return to the center to discuss the findings. When they return, the communication can take place in the most sensitive manner possible, with an individual specifically prepared to discuss the test results with the donor. If the donor elects not to return to the center for this meeting, we would then send the donor a more specific letter outlining the test results.

We assume that this approach would be acceptable under the proposal, but we urge FDA to specify that they will grant donor centers the flexibility to manage the donor contact and notification in a manner that allows maximum sensitivity for the communication. Thus, we appreciate clarification that a general letter followed by a more specific discussion or more specific letter, is acceptable.

3. Notification of Donor Reentry

The proposed regulation includes provisions for notifying the deferred donor of possibilities for reentry. This is contained in the CFR's description of the notification information. Specifically, Section 630.6(b)(5) states that the notification should define "Where applicable, the possibility that the donor may be found suitable for future donations."

Red Cross understands FDA's reasons for adding this requirement. Identifying and maintaining an adequate donor population has been the subject of considerable discussion within many forums, including Blood Products Advisory Committee, at Congressional Hearings, and at HHS Committee meetings. Red Cross and other blood banks are acutely aware of this need and have made substantial efforts to seek new donors and maintain good relationships with return donors.

Thus, we see FDA's requirement to indicate the possibilities for reentry as striving to support these efforts. The Agency also appears to be providing the blood centers with some flexibility by adding the term "Where applicable" to the requirement. However, we request that FDA rescind this proposed requirement for the following reasons.

Donor deferral notification must be made quickly, but donor reentry decisions are more operationally difficult, and often require additional evaluation time. We do not wish to risk an erroneous reentry decision due to the need for quick deferral notification when more deliberate consideration of the donor's reentry status is appropriate. For example, the donor center may wish to examine the need for additional tests prior to discussing reentry and such an evaluation should not impede the deferral notice.

Moreover, the criteria for reentry may change over time. We might find that although reentry was possible at the time of deferral, the criteria change a few months or years later on, making the donor ineligible, contrary to the letter they received at time of deferral. ARC prefers not to have to tell a potential donor "we've changed our mind".

Finally, Red Cross and other blood establishments are continuously seeking mechanisms to encourage donors to return. We are well aware that it is in our best interest and that of our customers and transfusion recipients to do so. Thus, while we appreciate FDA's positive intentions, we will continue to seek donors in what ever manner is both ethical and practical. Thus, this requirement is unnecessary to meet FDA's goal to maintain as large a donor population as possible and we ask FDA to allow donor centers to make determinations regarding re-entry decisions rather than including it in the regulation.

4. Syphilis

FDA has noted that deferral based on testing for syphilis is the subject of considerable debate. On page 45359 the agency states:

> the proposal to defer donors who test reactive for syphilis is subject to change pending the outcome of the request for comments on the value of donor testing for syphilis in the proposed rule on donor testing.

Red Cross agrees that this is an appropriate step to take. At FDA's public meeting On November 22, 1999 Red Cross presented the results of a pilot study that supports

reconsideration of the requirements for syphilis testing. Additionally, in a separate letter to FDA commenting on the proposal for testing requirements, we have included such data. [Docket # 98N-0581] Thus, Red Cross is also attaching the Syphilis testing data to the rulemaking record for the donor notification rule that is the subject of this letter. Should FDA decide to revise the requirements for Syphilis testing, ARC suggests revising all other donor regulations accordingly.

5. Recommendations vs. Requirements

One general comment Red Cross has is that there are some "recommendations" included in the preamble of the rule that are not specified in the regulatory text. (Some examples, such as FDA's recommendation to discuss "actions to minimize the risk of transmission" and to provide "the location of public health clinics as well as alternative testing and counseling centers" are discussed in greater detail in these comments.) This is potentially confusing to blood centers who are attempting to ensure compliance, and to FDA investigators who are conducting inspections. If FDA "recommends" certain aspects in the preamble, but does not specify them in the coded text, are they required or not? Between now and finalization of the regulation, we urge FDA to clearly state that a recommendation in the preamble is not the equivalent of a requirement in the regulation.

6. Evidence of Permanent Address

The regulation proposes that "blood and plasma establishments would be required to maintain records of the donor's permanent address. Donors should provide proof of a 'permanent fixed address.' Individuals who do not have evidence of a current address or who merely provide an address of a known or obviously transient nature should not be accepted as donors."(page 45360) The Red Cross agrees it is important for a blood collection establishment to know how to reach a donor quickly in case a deferral must be made following a collection. Indeed, this is the primary purpose of obtaining the address. However, we believe that requiring proof of a permanent address from a donor is not the best method to answer that need. In fact, the Red Cross believes that both the number of donor notifications that never reach the intended party, and the number of unnecessary deferrals, will increase if such a requirement is implemented.

a. Goal of Requiring the Address

The main purpose of obtaining the address is to be able to identify a stable location for a specific period of time that is suitable for notification purposes. Therefore, the Red Cross does not accept anyone who wishes to become a donor if they do not provide an address. However, a provable "permanent address," often will not fill that purpose. Donors may have privacy concerns or personal reasons for providing an address that, while still valid, differs from their provable permanent address. For example, a donor on extended business travel might be residing in temporary housing. They may have the post office holding or forwarded their mail which could substantially delay receipt of a notification. In such cases, obtaining their temporary address is more important. They may have no means of providing "proof" and it is not "permanent" as proposed.

There are many other situations where a temporary address is preferable. For example, college students may have a dormitory address during the school year, but consider their parent's home address to be the "permanent fixed address". Yet, their temporary address is where a notification should be sent, not to a parent's home.

Other special populations, such as religious groups that do not obtain or use driver's licenses or resident aliens or may not have a proof of their permanent address. Denial of these potential donors may be viewed as an inequitable screening practice. Similarly, not all states allow individuals of donation age, 17 or older, to drive. Some require waiting until age 18 and the driver's license is often the only means of establishing a permanent address. These younger individuals are especially encouraged to donate since they often become donors for life based on their earliest experiences. To add a requirement they may find discouraging at this early stage, or that would defer them would be a disservice to both the donors and the potential transfusion recipients. We've also noted that although this statement was made in the preamble to the rule, the regulatory text does not discuss the donor's address. We request that FDA eliminate the discussion of the donor's address from the preamble of the final regulation for the following reasons.

b. Relationship to Other Donor Questions

The proposed requirement for proof of a permanent, fixed address, differs significantly from the other donor information required before collection. The Donor Health History interview relies on the donor to provide accurate and complete information, without

proof. In terms of the donor's eligibility, the health history is a more important criterion than their address. We believe that the same reliance should also apply to the donor's address.

c. Definition and Documentation of "Permanent Address"?

The terms "Permanent Address" and "Permanent Fixed Address" are used interchangeably in the proposed rule. Moreover, they are not defined. A clearer definition would be advisable if this proposal is to become part of the regulation to avoid varying interpretations by both blood collection establishments and by FDA inspection personnel. However, we do not believe that definitions that fit all possible donation circumstances are feasible.

A driver's license is typically used as an appropriate form of "proof". But if a potential donor does not happen to have one with them at the time of donation, is a "verification" by a friend or co-worker sufficient proof? If the license is expired, can it still be used as proof? If the donor has recently relocated but has not updated their address on their license, should they be deferred? Red Cross believes that these individuals are appropriate donors and that these forms of ID would be acceptable, but there would be considerable uncertainty under this proposal as to whether the Agency and each individual investigator would agree.

Clearly there are numerous exceptions and contingencies that would need to be defined under the proposal for proof of a "permanent address." Rather than ask donor centers to revise SOPs to cover all such contingencies, it would be more efficient to avoid entering this requirement into the final rule.

7. Permanent deferral due to donor suitability criteria

Part 630.6 of the proposed rule requires donor notification for all donors who are "deferred based on results of tests for infection with a communicable disease agent . . . or based on deferral for suitability criteria." The Red Cross understands that the agency intends to "identify donor suitability criteria that would cause a donor to be deferred and thus trigger notification under" this proposed rule. However, without specifying what suitability failures require description in the notification, ARC cannot fully evaluate the impact of this rule.

ARC noted the recommendation that "notification be based on positive confirmatory tests for viral markers . . . and all other medical reasons that result in permanent deferral." However, some medical reasons for permanent deferral are not communicable diseases and are not transmissible via transfusion. Multiple Sclerosis and Typhoid, for example, are not "communicable" and are not transfusion "transmissible". Therefore, the Red Cross believes that a requirement to notify can be based on "suitability criteria" but the content of the notification should be limited in scope to test results, and to specific behavior that increases risk for diseases known to be transmitted by transfusion such as hepatitis and HIV. Details of "all other medical reasons" can not be fully known to the blood center, and should not be provided in the notification.

8. Donor Notification Contact Requirements-Timing and Methods

The proposed rule (part 606.100) requires that establishments develop standard operating procedures for donor notification to include "procedures for the appropriate follow up if the initial attempt at notification fails . . .." Part 630.6 (c), further states that the notification process shall include a minimum of three attempts to notify the donor and be completed within 8 weeks after the determination that the donor should be deferred . . .." While Red Cross agrees that if an initial attempt is not successful, additional attempts should be made to notify the donor. However, ARC also believes that upon sending a notification, additional notification attempts required to meet the "minimum of three attempts" are unnecessary unless there is reason to believe it has not reached a donor. In some cases, donors do not acknowledge receipt of notification, and as written, the proposal could require "call backs" or other attempts to seek out a donor because of lack of acknowledgement, not lack of receipt. Red Cross suggests revising this statement to clarify that if a blood bank sends the first or second notification, no subsequent attempts are necessary.

The proposed rule also implies that notification attempts should be made using registered mail. The Red Cross has found that some donors, due to legal or financial issues, deliberately avoid accepting registered or certified mail. Or, if received, they may choose not to return for a face-to-face discussion of the test results. Since the decision to respond to a notification is solely up to the donor's discretion, Red Cross believes these situations should not be regarded as requiring further follow-up.

The Red Cross believes that the requirement to develop a donor notification procedure establishes the standard by which each establishment can be held accountable. The rule clearly states that a procedure which outlines donor notification tasks is required and that it must address appropriate steps to take when an initial attempt at notification fails. ARC believes that FDA review of this procedure is the appropriate level of oversight for the performance of donor notification tasks. ARC feels that the proposed rule should describe the need to perform donor notification without further specification of requirements for how to perform the associated tasks. Otherwise, the rule may result in less efficient methods or timeframes due to the need to meet "requirements" without the intended safety that FDA is trying to achieve.

Red Cross notes that the proposed donor notification requirements are more specific than any we are aware of for a patient who tests positive for specific diseases when under a physician's care. Physicians and other health care providers are not subject to similar regulations despite their more direct responsibility for the patient's outcome. We believe it is inappropriate for the agency to propose more rigorous requirements for blood establishments than what is routinely expected for health care providers who direct patient care.

9. Notification for repeatedly reactive (RR) on a single occasion for HTLV, types I and/or II or for Anti-HBc.

ARC believes it is appropriate to notify donors who test RR on a single occasion for Anti-HBc or HTLV, types I and II. The Red Cross does notify donors who test RR on a single occasion for both screening tests. Donors who test as RR on a single occasion for Anti-HBc or HTLV, types I and II, are placed in a surveillance category and are not deferred. We place them in this category since there is not currently available an approved supplemental test to aid in the deferral decision making. Although ARC has chosen to notify donors, ARC agrees with the agency's proposed Section 610.41 (b) to allow blood centers the flexibility to chose to notify donors testing RR for HTLV types I and II or anti-HBc as donors of Source Plasma.

10. Deferral at collection site

Current Red Cross practices allows collection staff to provide a generic, permanent, or temporary deferral letter to donors who fail donor suitability criteria while the donor is at the collection site. This generic letter directs the donor to contact trained donor suitability staff or their health care provider if they have additional questions or concerns.

This immediate notification is beneficial in that there in no "lag" time between the deferral and the notification.

Although the generic letters do not state the specific reason for deferral, the reason is discussed with the donor during the health history interview. Information recorded on the Blood Donation Record (BDR) serves as the documentation of the deferral.

Implementation of the proposed rule, however, will fundamentally change this process. Health counseling, medical referral, suitability for future donations are not typically discussed during the deferral process given the training levels of staff and resources currently available on collection sites. Requirements for these activities at a collection site would necessitate the addition of staff trained in counseling and staff with more medical expertise than is generally used. This not only would change the entire collection setup, the collection environment is not an appropriate or a comfortable place for this type of interaction with a donor. In addition, counseling a donor at a collection site would not allow a review of a donor's medical history or donation history, including whether the donor was previously counseled. Thus, the counselor could be missing important information that should affect any interaction between a counselor and a deferred donor.

Thus we urge FDA to amend the proposed requirements, particularly for counseling, medical referral, and suitability for future donations so that we may continue the practice of immediate deferral.

11. Cost Estimates

As FDA notes, a cost impact assessment is required under the Regulatory Flexibility Act. However, the estimates of the costs involved with the transition from the current notification system to the one proposed are far more significant than FDA's analysis indicate.

For example, the estimate of 4 hours to revise SOPs if the donor center is substantially in compliance with the proposal, and 24 hours if further revisions are necessary, is a significant underestimate of the time required to perform the changes. The review of the regulation alone would require at least 4 hours for an individual staff member to perform in order to comprehensively understand the directives.

After that, a careful cross comparison of the new regulation with the existing SOPs, followed by development of SOP revisions would be the next step. Most SOP

revisions, even if the blood center is substantially following the requirements, cannot be accomplished in only 4 hours. Every letter will need to be reviewed and potentially revised. Blood centers will also need to revise computer software to ensure appropriate letter preparation and documentation, there will be staff training in order to follow the new SOPs and use the revised software. Blood centers will also evaluate their need for new equipment such as printers, and all SOP, software, and letter revisions will need review to ensure complete and accurate compliance without risk of either donor resistance or adding liability to the center.

ARC suggests that FDA reevaluate the regulation's impacts to help ensure that final decisions are the most appropriate for aiding the safety of the blood supply and the donors.

Conclusion

The Red Cross appreciates the opportunity to submit its views on the Guidance to the FDA. If there are any questions on this letter, please contact Anita Ducca, Director, Regulatory Relations, at 703-312-5601.

The following attachment has been submitted to Docket number 98N-0581.

It is also being submitted to Docket No. 98N-0607.

Syphilis Testing

ARC supports FDA's efforts to review relevant data and consider eliminating the requirement for syphilis testing. ARC also acknowledges that sufficient data will be required as described in section A on p. 45342 and 45343:

> If the agency receives comments with adequate data ... FDA may proceed with rulemaking to remove the requirements for a serologic test for syphilis...

Red Cross has begun research that we believe will support this step. Our initial findings were presented at FDA's meeting on this proposal held at NIH on November 22, 1999, and at a private meeting with FDA/CBER staff on December 15, 1999. We have provided a summary description of our findings below and have attached copies of our presentation materials for additional review by FDA.

We recognize that accurately assessing the value of blood donor serological testing for syphilis in relation to transfusion safety and public health will require extensive quantitative data from multiple sources. Our concerns with blood donor syphilis testing in its present format primarily arise from the very poor predictive value of the test for active syphilis infection. As a result, a very difficult and upsetting result notification message that must be provided to the vast majority of seropositive donors who have never had syphilis infection, or experienced infection many years ago that has long since been treated.

The aspects of this issue that we have explored include: 1) the prevalence of reactive screening tests and positive confirmatory tests among blood donors in our system; 2) the extent to which FTA-ABS confirmed serology among random blood donors does, or does not reflect the presence of circulating T. pallidum DNA; and 3) the relationship of a reactive syphilis serological screening test to unreported behavioral risk in active donors. In the interest of increasing the scientific knowledge base about the potential for transfusion-transmitted syphilis in the US, ARC is willing to consider the funding and implementation of additional studies to expand our current pilot data regarding infectivity of seropositive donor samples, as evidenced by the presence of T. pallidum DNA and RNA. As discussed during the 12/15 meeting with CBER staff, a final sample size for these studies of n = 1000 samples will constitute a sample that is likely to provide infectivity estimates that are reasonably reliable from a statistical standpoint. To examine the possibility of a surrogate relationship between blood donor syphilis seropositivity and infection with other transfusion-transmissible infection, the ARC ARCNET program has also begun an analysis of its systemwide epidemiologic database to determine the extent to which syphilis seropositivity is predictive of prevalent and/or incident HIV, HTLV, HCV, and HBV infection.

Blood Donor Syphilis Testing in the ARC System
Susan Stramer, Ph.D, ARC National Confirmatory Testing Laboratory

All donated blood is screened for total antibody to T. pallidum by PK-TP (PK7200 Olympus). Repeatedly reactive samples are confirmatory tested by FTA-ABS (Zeus) to an interpretation of Positive (2-4+), Minimally Reactive (1+), or Negative. Non-negative samples are then tested by RPR to assist donor notification of test results. Trends in seroprevalence for each of these assays are provided in the attached data sheets.

Relationship of anti-HBc and Serologic Tests for Syphilis (STS) to Blood Donor Behavioral Risk Factors. A.E. Williams, K. Watanabe, D. Ameti, S. Kleinman, M. P. Busch, S. Orton, G. J. Nemo. NHLBI REDS Study, Rockville, MD

Donor screening tests for anti-HBc and STS have limited value for prevention of post-transfusion hepatitis B and syphilis. It is unknown whether these tests have any value for identification of unreported donor risk behaviors. Anonymous mail surveys to measure donor characteristics and deferrable risk (DR98) were administered to 92,581 recent donors at eight blood centers from 4/98 through 10/98. The survey sample was weighted to over-represent anti-HBc+ and STS+ donors and surveys were pre-coded to reflect these results. Odds ratios comparing DR98 among anti-HBc+ and STS+ donors vs. seronegative donors were tested by Chi-Sq.

DR98 prevalence among respondents (weighted data) was 2.9% among 50,267 seronegative donors, 8.0% among 1726 anti-HBc+ donors (OR=2.9; $p< 0.001$), and 13.7% among 414 STS+ donors (OR=5.5; $p<0.001$). When the donor screening questions related to history of syphilis or treatment for syphilis were removed from the deferrable risk calculation however, deferrable risk in STS+ donors was no higher than the risk in seronegative controls. Because STS+ and anti-HBc+ seroprevalence in the donor pool is low (0.14% and 0.7% respectively), these tests eliminate only a small proportion of total deferrable risk in the unscreened donor pool (1.0% and 2.2% respectively).

Prevalence of *T. pallidum* DNA in the Blood of Donors Who Are Confirmed Positive by Current Serological Tests for Syphilis
SL Orton, MSPH, PhD candidate, RG Cable, MD, AJ Grindon, MD
AE Williams, Ph.D. American Red Cross ARCNET Program
Hsi Liu, Ph.D, Centers for Disease Control and Prevention

Based upon the hypothesis that the blood of STS reactive, FTA-ABS reactive donors does not differ from seronegative controls in terms of syphilis infectivity, our study goal was to determine (on a pilot basis) whether STS reactive, FTA-ABS reactive donors showed any evidence of circulating *T. pallidum* DNA. The sample size tested included 100 STS reactive, FTA-ABS samples; 50 of which were RPR reactive, 50 RPR nonreactive. Aliquots from existing platelet concentrates (PC) from these donors were tested for *T. pallidum* DNA using two PCR test methodologies. The first PCR test is specific for *T. pallidum* and sensitive to 25 organisms per 100 ul of extracted material; the second PCR test is a multiplex test that includes testing for *T. pallidum* DNA and is sensitive to 10 organisms per 100 ul of extracted material. Negative and positive external controls were tested. The positive external control was prepared by spiking a 100 ul sample aliquot from an STS nonreactive platelet concentrate with ~50 organisms. All 100 samples were negative for *T. pallidum* DNA by both PCR tests, and all external control results were appropriate. The study had several limitations which included (1) fresh whole blood is a preferable sample, although PC's were adequate for this study, (2) DNA testing cannot differentiate between live and dead organism (not relevant to these results) and (3) in a study of sample size 100 and all negative test results, there is up to a 3% chance that there is an incorrect interpretation of no infectivity. We concluded that we could not demonstrate circulating *T. pallidum* DNA in STS reactive, FTA-ABS positive blood donors. Further work will include RT-PCR testing for RNA (a more sensitive methodology), and should include further study with a larger sample size.

Prevalence of circulating *T. pallidum* DNA in STS+/ FTA•ABS + blood donors:

- American Red Cross ARCNET Program
  - SL Orton, MSPH, PhD candidate
  - RG Cable, MD
  - AJ Grindon, MD
  - AE Williams, Ph.D.
- Centers for Disease Control and Prevention
  - Hsi Liu, Ph.D.

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Factors that influence an infected individual (with spirochetemia) presenting as a blood donor include:

Symptomatology

Incidence

Background

- Primary syphilis: chancre/acute local lymphadenopathy present (97%/80%) ~ 3 weeks after exposure with subsequent organism infiltration of the blood stream. Resolution of the chancre occurs at ~ 6 weeks.
- Secondary syphilis: infiltration of the blood stream (and peak spirochetemia) causes systemic macropapular rash development in ~ 100% of infected individuals (~ 6 weeks after exposure), with gradual clearing of the spirochete.

2

The phases overlap.

continued

- It is unlikely that an individual would be asymptomatic during spirochetemia.
- Rabbit infectivity tests indicate that with disappearance of overt symptoms, the blood loses its ability to infect due to migration of the spirochete to the lymphoid tissue.
- STS are positive except very early in the primary phase.

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continued

- CDC reported that in 1998:
  - 87% decline in incident syphilis cases between 1990 (20.6/100,000) and 1998 (2.6/100,000)
  - 14 states reported < 5 cases; 5 states reported 0 cases
  - 78% (2430/3115) US counties reported 0 cases
  - 50% of incident cases occurred in 0.9% (31/3115) US counties

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ARC statistics

- 1,801,505 allogeneic donations tested by PK-TP (after diluent modification) between May 1993 and September 1995; representing 16% of total blood collected
- 2151 (0.12%) STS reactive; 1274 (0.07%) confirmed by FTA-ABS
- 6,000,000 donations annually:
  - ~7,200 lost components
  - ~4,200 temporarily deferred donors

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How does syphilis testing impact the ARC?

This data is extracted from a paper by Aberle-Grasse (ARCNET) in Transfusion, 2/99

Goal

Determine if there is any evidence of circulating *T. pallidum* in the blood of donors who are STS reactive, FTA-ABS reactive.

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Methods: ARC laboratory infectivity study

- Target sample size: 100 STS reactive, FTA-ABS reactive donations; 50 RPR reactive, 50 RPR non-reactive (including 16 autologous)
- Collect and freeze daily (within ~24 hours) any existing platelet concentrates from PK-TP (Olympus Corp) reactive blood donations. Ship to HL.
- Upon receipt of confirmatory test results, aliquot platelets and send for DNA testing (maximum of 2 freeze/thaw cycles).

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NE: MA, ME, VT, NH:	5 samples
CT:	7
Southern: GA, South Florida	23, 52
GCP: DC, MD	13

Testing

- PCR for *T. pallidum* specific DNA
  - pol A gene target: 378 bp band
  - capillary electrophoresis and fluorescent detection
  - read on an ABI 310 Genetic Analyzer
  - sensitivity as low as 25 organisms/100 ul platelet concentrate extracted

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continued

- Multiplex PCR kit (Roche) for *T. pallidum, H. ducreyi* and Herpes Simplex Virus type 1 and 2.
  - 47kd basic membrane protein gene target for *T. pallidum* previously described.
- Both assays included internal and external control samples. Positive external controls were diluted to 50 organisms per 100 µL from stock *T. pallidum* (Nichols strain) cultures.

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Same sample volume was used.

Results

- All 100 samples tested negative for *T. pallidum* DNA by both assays.
- Internal and external control samples results were appropriate.

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Study limitations

- The optimal sample is fresh whole blood.
- One weakness of DNA detection is the inability to differentiate live from dead organisms.
- Because we can never "prove" a negative test result, in a pilot study with a sample size of 100 and all negative test results, there is up to a 3% chance that there is an incorrect interpretation of no infectivity.

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The spirochete can tolerate ~3% oxygen tension and then will die ~12 hours. The oxygen tension of the platelet concentrate bag is ~15%. This is probably not the component we should be concerned about.

For the purposes of our study, however, the slow spin separation of platelet rich plasma followed by the hard spin preparation of the platelet concentrate would yield spirochetes in the platelet concentrate bag. In addition, *T. pallidum* DNA is an extremely stable biopolymer.

Conclusions

- We did not demonstrate circulating *T. pallidum* DNA in STS reactive, FTA-ABS reactive blood donors in this study.
- Because of the low incidence of syphilis in the population, it is unlikely that an infected individual would present as a blood donor.

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From the literature:

The low incidence of disease in the US population (and the demographics of individuals currently found to be infected with syphilis) make it unlikely that an infected individuals will present as a blood donor.

Conclusions continued

- It is unlikely that a symptomatic individual would present as a blood donor.
- The data suggests that in the absence of syphilis testing, transfusion transmitted syphilis infection is unlikely to occur.

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From the literature:

Due to the symptomatology of this disease during peak spirochetemia (secondary phase), it is unlikely that a symptomatic individual would donate.

AND

Current information regarding spirochete survival (or lack thereof) in the various blood components, coupled with a lack of evidence that confirmed positive blood donors actually have spirochetemia, makes the potential risk of transfusion transmitted syphilis small.

Relationship of anti-HBc and Serologic Tests for Syphilis (STS) to Blood Donor Behavioral Risk Factors

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Retrovirus Epidemiology Donor Study (REDS)

Background - anti-HBc

- Assays for anti-HBc have low specificity and high donor loss (0.7 - 1.8%) when used for screening of donated blood
- Value of anti- HBc for detection of HBV infection is limited
- Surrogate value of anti-HBc for behavioral risk detection is speculative

Background - STS

- Current STS assays detect long term *T. pallidum* antibodies in 0.1 - 0.2% of healthy blood donors.
- No well-documented cases of transfusion-transmitted syphilis have occurred in the US in over 30 years
- Surrogate value of STS for behavioral risk detection is speculative

Background - STS (cont.)

- 1995 NIH Consensus Conference debated the value of continued blood donor STS screening
- August 1999: FDA seeks data regarding the value of donor STS (Proposed Rules: Requirements for testing....)
  - as a marker of high risk behavior
  - as a surrogate test for other infectious diseases
  - in preventing the transmission of syphilis through transfusion

Study Objective

- Assess the value of anti-HBc and STS as surrogate indicators of blood donor risk behaviors

REDS 1998 Donor Survey

- ARC, Greater Chesapeake and Potomac Region
- ARC, Southeastern Michigan Region
- ARC, Southern California Region
- Blood Centers of the Pacific - Irwin/UCSF
- Oklahoma Blood Institute
- New York Blood Center
- Blood Bank of San Bernardino
- Lifeblood (Memphis)
- Medical Coordinating Center - Westat, Inc.

REDS 1998 Donor Survey (cont.)

- Anonymous mail survey
- Allogeneic donors; ≥18 years.
- Monthly probability sample of donors April through October 1998.
- 92,581 sampled donors at eight sites
- 57% survey response rate

REDS 1998 Donor Survey (cont.)

- Survey sample included four laboratory test strata:
  - anti-HBc+
  - STS+
  - other lab reactivity
  - seronegative
- all anti-HBc+ and STS + donors surveyed

REDS 1998 Donor Survey - Content

- Demographics
- Donation history/experiences
- Deferrable Risk Assessment (DR)
- Multiple Investigations
  - » Surrogate value of STS and anti-HBc
  - » Incentives
  - » Hemochromatosis
  - » HIV test-seeking

Deferrable Risk

- A risk that should have resulted in deferral according to blood donor screening criteria at the time of the survey

Results: Deferrable Risk (DR)

	DR Prev	OR	Adj.OR*
◆ Neg	2.9%	1.0	1.0
◆ anti-HBc	8.0%	2.9†	2.7†
◆ STS+	13.7%	5.4†	5.5†
◆ Other+	11.5%	4.4†	3.3

* Odds ratios adjusted for gender, age, race/ethnicity, education, center, FT donors (all $p < .001$)

† $p < 0.001$

Proportion of Overall DR Associated with anti-HBc and STS (%)

	DR Prev	% of Overall DR
◆ Neg	2.9	94.4
◆ anti-HBc	8.0	2.4
◆ STS+	13.7	1.0
◆ Other+	11.5	2.2

Proportion of Overall MSM and IDU Risks Associated with anti-HBc and STS (%)

	MSM	s/MSM	IDU	s/IDU
◆ Neg	94.1	96.5	87.0	93.7
◆ anti-HBc	3.0	2.1	2.5	1.9
◆ STS+	0.3	0.5	0.2	0.5
◆ Other+	2.6	1.0	10.3	3.9

STS-Related Risks Included in Deferrable Risk Calculation

Q48. In the past 12 months, have you had a positive test for syphilis?

Q49. In the past 12 months, have you had or been treated for syphilis or gonorrhea?

Results: Deferrable Risk (DR) excluding STS

	DR Prev	OR	Adj.OR*
◆ Neg	2.7%	1.0	1.0
◆ anti-HBc	7.3%	2.8†	2.5†
◆ STS+	4.7%	1.7‡	1.3
◆ Other+	11.5%	4.6†	3.6‡

* Odds ratios adjusted for gender, age, race/ethnicity, education, center, FT donors (all $p < .001$)

† $p < 0.001$; ‡ $p < 0.05$

Summary: Surrogate value of anti-HBc+

- When controlled for FT donor status and demographic factors, anti-HBc+ donors have a 2.7-fold higher level of reported deferrable risk than seronegative donors.
- Qualitatively, anti-HBc-associated risks are similar to those of the overall donor base
- When anti-HBc prevalence (0.7%) is considered, anti-HBc+ is associated with 2.4% of overall DR

Conclusion: Surrogate value of anti-HBc+

- The value of anti-HBc as a surrogate needs to be considered in the context of other variables that have modestly higher levels of deferrable risk. (males, FT donors, etc.)

Summary: Surrogate value of STS

- When controlled for FT donor status and demographic factors, STS+ donors have a 5.2-fold higher level of reported deferrable risk than seronegative donors.
- When STS+ prevalence is considered (0.14%), STS is associated with 1.0% of overall DR)

Summary - Surrogate value of STS (cont.)

- However, deferrable risk associated with STS+ is largely due to STS-related risk factors.
- When STS-related risk factors are not considered, STS has no significant value as a surrogate indicator of behavioral risk

Conclusion

- **If molecular studies continue to show an absence of *T pallidum* in STS+ blood, the requirement for STS testing of donated blood should be removed.**